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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/525,679 | 02/17/2005 | Hae-Young Suh | DE1617 | 3749 |

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| EXAMINER | |
|---|---|
| MONTANARI, DAVID A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

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| 12/29/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/525,679 | SUH ET AL. | |
| | Examiner | Art Unit | |
| | David Montanari | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicants arguments filed on 9/9/2008 have been entered.

2. The rejection of claims 1-4 under 35 USC 103(a) is withdrawn in view of Applicants arguments. However a new 35 USC 103(a) rejection is made below.

3. Claims 1-8 are examined in the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbury et al. (2000, J. Neuroscience Res., Vol. 61, pgs. 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364).

The specification teaches on pg. 1 line 13 that "Mesenchymal stem cells (MSC) are multipotent bone marrow stromal cells aiding hematopoiesis". For the purposes of this rejection, the bone marrow stromal cells that are differentiated into neuronal cells taught in the art below are applicable over the claimed MSC's of the invention.

Woodbury et al. teach that human bone marrow stromal cells (MSC) have the capacity to differentiate into neurons (pg. 364, Abstract). Woodbury continues to teach that human MSC neuronal induction was carried out by culturing said cells in media

comprising DMEM, 1-10 mM of BME (pg. 365 col. 1 parag. 1) and 10 μM of forskolin (pg. 365 col. 1 parag. 5 last sentence). Woodbury concludes by teaching they are the first to report that peripheral mesenchymal stem cells can differentiate into neurons in vitro and that MSC's may be useful in the treatment of a wide variety of neurologic diseases (pg. 369 col. 1 parag. 2). Woodbury does not teach a method of transdifferentiating MSC into neuronal cells using bHLH transcription factors.

However, at the time of filing it was known in the art that bHLH transcription factors played a significant role in the determination of neuronal fates in cells. Guillemot F. teaches that “proteins of the bHLH class have central role in the determination of neuronal lineages in the peripheral and central nervous system and in the acquisition of pan-neuronal traits by differentiating neurons" (pg. 357 col. 1 parag. 1 lines 6-11). Guillemot continues to teach that a large number of transcription factors are sequentially and transiently expressed in neural precursor cells as neurogenesis proceeds and that the bHLH class of transcription factors play a important role in cell-type specification (pg. 357 col. 1 parag. 1 lines 1-3 and col. 1 last two lines bridge col. 2 parag. 1). Guillemot continues that a variety of bHLH genes such as neurogenin, MASH1, MATH3, neuroD and neuroD2 are expressed in a wide variety of cells that will commit to a neural lineage (pg. 357 col. 2 last sentence bridge pg. 358 col. 1 parag. 1 and Fig. 1). Guillemot concludes that "by controlling the ability of neural progenitors to respond to extrinsic factors, bHLH proteins may play an important role in integrating signals from the environment into transcriptional programs of differentiation” (pg. 361 col. 2 parag. 1 last sentence).

Thus it would have been prima facie obvious to ordinary artisan at the time of filing to combine the teachings of Woodbury teaching that MSC have the capacity to differentiate into neurons and that they would be useful for the treatment of a variety of neurological diseases with the teachings of Guillemont teaching that bHLH transcription factors have a central role in determining neuronal cell differentiation to transdifferentiate MSC into neuronal cells by increasing a bHLH transcription factor in a MSC. Additional motivation is provided by Guillemont in teaching a variety of bHLH transcription factors including neurogenin, MATH3 and MASH1.

Thus the cited art clearly provides a case of prima facie obviousness.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbury et al. (2000, J. Neuroscience Res., Vol. 61, pgs. 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364) as applied to claims 1, 2, 5 and 6 above, and further in view of Elwood et al. (1998, Blood, Vol. 91, pgs. 3756-3765).

Woodbury and Guillemot combined teach a method of using bHLH transcription factors to transdifferentiate MSC. Woodbury and Guillemot do not teach a method of transducing MSC with a viral vector coding for a bHLH transcription factor.

However at the time of filing it was known in the art that it was routine to use viral vectors to transduce cells. Ellwood et al. teaches that the product of the SCL gene is a bHLH transcription factor that is essential for the development of hematopoietic stem cells (pg. 3756, Abstract). Ellwood continues to teach that in order to force expression of SCL in CD34+ cells isolated from human bone marrow, an SCL retrovirus was used to

transduce said cells (pg. 3756, Abstract and pg. 3760, col. 2, parag. 2, 2nd to last sentence).

Thus it would have been prima facie obvious to the ordinary artisan at the time of filing to combine the teachings of Ellwood regarding the utility of using retroviral vectors to transduce cells with a bHLH transcription factor with the teachings of Woodbury and Guillemont regarding a method of transdifferentiating MSC into neuronal cells to transduce a bHLH transcription factor in a viral vector into a MSC to transdifferentiate said MSC into a neuronal cell.

Thus the cited art clearly provides a case of prima facie obviousness.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbury et al. (2000, J. Neuroscience Res., Vol. 61, pgs. 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364) as applied to claims 1, 2, 5 and 6 above, and further in view of Zou et al. (2002, J. Neuroscience, Vol. 22(12), pgs. 4833-4841).

Woodbury and Guillemot combined teach a method of using bHLH transcription factors to transdifferentiate MSC. Woodbury and Guillemot do not teach culturing MSC in medium supplemented with N2.

However at the time of filing it was known in to be routine in the art to use N2 supplement when culturing neuronal cells. Zou et al. teach a method of culturing cerebral cortical neuronal cells with N2 supplement (pg. 4834 col. 1 parag. 2). Zou

continues to teach that they used N2 supplements because it inhibits neuronal death (pg. 4835 col. 2 parag. 2).

Thus it would have been prima facie obvious to the ordinary artisan at the time of filing to combine the teachings of Zou regarding using N2 supplement in culture media to prevent neuronal cell death with the teachings of Woodbury and Guillemot regarding a method of transdifferentiating MSC into neuronal cells to use N2 supplement in culture media to prevent the death of newly transdifferentiated neuronal cells.

Thus the cited art clearly provides a case of prima facie obviousness.

## *Allowable Subject Matter*

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 7 is free of the prior art.

## *Conclusion*

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632